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Demographic characteristics of the COVID-19 vaccine trial participant population, mortality population, and individuals fully vaccinated in the United States: A comparative analysis

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Demographic Characteristics of the COVID-19 Vaccine Trial Participant Population, Mortality Population, and Individuals Fully Vaccinated in the United States: A Comparative Analysis

by

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Abstract

The purpose of this study was to compare the demographic variables of three populations, COVID-19 vaccine trial participants, COVID-19 deaths, and individuals vaccinated for COVID-19, to determine if the trial participants were appropriately representative. Demographic data (age, sex, race and ethnicity, and presence of comorbidities) were collected from publicly available datasets, organized, and compared. The demographic characteristics of the vaccine clinical trials participants were comparable to those who died due to COVID-19, but less comparable to those who were the first to receive a COVID-19 emergency-use-authorized vaccine.

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Introduction

Clinical trials are imperative to determine the safety and efficacy of new drugs, biologics, and medical devices. Because people of different subgroups may have various responses to medical treatments, it is crucial to test investigational products in a variety of populations (U.S. Food & Drug Administration, 2014), and the coronavirus disease 2019 (COVID-19) vaccines are no exception.

Background

COVID-19, also known as, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China, in December 2019 (Centers for Disease Control and Prevention, 2021d). The COVID-19 outbreak quickly spread worldwide. On March 11, 2020, World Health Organization (WHO) director-general, Dr. Tedros Adhanom Ghebreyesus, publicly declared COVID-19 a global pandemic. Pharmaceutical companies understandably did not hesitate and promptly began research on treatments and vaccines for the novel coronavirus. Due to the urgency that accompanies a pandemic, clinical trials and overall recruitment of participants were accelerated. This made it possible for the Food and Drug Administration (FDA) to authorize three COVID-19 vaccines for emergency use quickly.

Pfizer-BioNTech and Moderna were the first two pharmaceutical companies that received FDA Emergency Use Authorization (EUA) of their mRNA vaccines in December 2020 (U.S. Food and Drug Administration, 2020a, 2020b). Soon after, Johnson & Johnson/Janssen (J&J) received FDA EUA for a single-dose vaccine in February 2021 (U.S. Food and Drug Administration, 2021). Each EUA was based on interim analyses of phase III, multicenter and international clinical trials, each consisting of thousands of participants (U.S. Food and Drug

Administration, 2020a, 2020b, 2021). As each of these clinical trials are following participants for two years after vaccine administration, each one has yet to conclude (U.S. Food and Drug Administration, 2020a, 2020b, 2021).

Although the FDA analyzes the diversity amongst clinical trial participants prior to authorizing the vaccines for emergency use, certain subgroups may be underrepresented. As a result, subgroups that are not appropriately represented in the vaccine clinical trials are receiving one of the three vaccines with the possibility of unknown risks.

Vaccine Distribution Plan

Upon the first EUA of a COVID-19 vaccine, the U.S. COVID-19 vaccination distribution program was initiated by the Advisory Committee on Immunization Practices (ACIP), as there was a limited supply (Centers for Disease Control and Prevention, 2021c). During the first phase, the ACIP prioritized health care personnel and residents and staff members of long-term care facilities (LTCF; Dooling et al., 2020). The ACIP is a group of medical and public health experts with the U.S. CDC that develops recommendations and guidance on effective control of vaccine-preventable diseases. As age is known to play a significant role in the severity of COVID-19 infection, the vaccine allocation plan advanced accordingly. In Phase 1b of the vaccine allocation plan, the vaccine was offered to individuals aged 75 and older and in Phase 1c, to people aged 65-75 years (Centers for Disease Control and Prevention, 2021c). The timeline of vaccine distribution is presented in Appendix A.

Adverse Events Targeting Subgroups

Individuals who receive a COVID-19 vaccine and their health care providers are strongly encouraged to report any adverse events they experience through the Vaccine Adverse Event Reporting System (VAERS). The purpose of VAERS is to detect possible safety signals by monitoring adverse events associated with vaccine use. The reports are monitored and reviewed by the CDC, the FDA, and the U.S. Department of Health & Human Services (HHS). This information is essential to assess relationships to the vaccines and ultimately determine potential risks associated. The adverse event (AE) reports described below are a few examples of potential risks that each seem to affect certain subgroups more than others:

1. Many reports of developing thrombosis with thrombocytopenia syndrome (TTS) following administration of the J&J vaccine. TTS occurs when a person develops blood clots (thrombosis) and a low platelet count (thrombocytopenia). The reports are occurring mostly in women younger than 50 years old (Centers for Disease Control and Prevention, 2021n). These concerning reports caused a temporary pause in administration of the J&J vaccine on April 13, 2021, only 6 weeks after it was authorized for emergency use. After further investigation, the use of this vaccine has since resumed, but the CDC now recommends that women under 50 consider other vaccine options currently available to avoid this risk (Centers for Disease Control and Prevention, 2021f, 2021n).
2. The CDC and FDA identified multiple reports of developing myocarditis and pericarditis, an AE that is occurring particularly in male adolescents and young adults, less than 30 years old (Centers for Disease Control and Prevention, 2021n). Most of these cases are occurring after an mRNA COVID-19 vaccination (Pfizer-BioNtech or Moderna).

Ongoing investigations are in progress to assess the relationship (Centers for Disease Control and Prevention, 2021n).

3. Reports of Guillain-Barre Syndrome (GBS), an overall rare condition, were identified (Centers for Disease Control and Prevention, 2021n). GBS is a condition in which the immune system attacks the nerves causing muscle weakness and sometimes paralysis. The cases have been predominately reported in men, aged 50 years and older, approximately two weeks after receiving the J&J vaccine.

Although these adverse events are considered rare, each of the AEs are recognizably occurring amongst certain demographic subgroups (e.g., women, adolescents, men). Therefore, recruiting and maintaining a diverse study population throughout a clinical trial is crucial to assess these differences in advance.

Diversity in Clinical Trials

There are many complex sources of racial and ethnic disparities in health care. According to Nelson (2002), historic and contemporary social and economic inequalities, as well as persistent racial and ethnic discrimination in many sectors of American life, are just a few contributing factors. The Nazi experiments and the Tuskegee syphilis study are two historical cases that may have initiated hesitation amongst minority groups to participate in clinical trials. When the Tuskegee Study was ruled “ethically unjustified,” an ethical and regulatory framework quickly began to take shape in the U.S (Centers for Disease Control and Prevention, 2021b). The Belmont Report (1978), written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, identifies basic ethical principles and guidelines that address the ethical issues, which arise from the conduct of human subjects research. To overcome health disparities, the National Institutes of Health (NIH) Revitalization

Act of 1993 published guidelines that would enhance the inclusion specifically of women and minorities in clinical research (National Institutes of Health, 1993). Although the preceding documents have created a structural, ethical, and moral framework, the main sources of guidance on the ethical conduct of clinical research were evidently written in response to specific events to avoid future scandals (Emanuel, 2000).

Unfortunately, patient barriers to trial participation still exist and are commonly reported as fear, mistrust of the medical community, and the overall burden associated with trial participation (Schmotzer, 2012). Aside from consciously avoiding participation, other barriers result in underrepresented minority groups in study populations, as well. Such barriers include physician reluctance to refer minorities to clinical trials, health illiteracy, and financial barriers, to name a few (Noah, 2003). Bias, stereotyping, prejudice, and clinical uncertainty on the part of health care providers may also contribute to these disparities (Nelson, 2002).

Van Spall (2007) demonstrated that women, children, the elderly, and those with common medical conditions are frequently excluded from randomized controlled trials (RCTs). In 81.3% of the RCTs that Van Spall analyzed, individuals were excluded from trial participation due to medical comorbidities alone. As the three COVID-19 vaccines are currently available to *all* adults in the U.S. (apart from Pfizer-BioNtech, which is now available to those aged 12 and older), it is important to understand the possibility that not *all* demographic characteristics were adequately represented in the vaccine trial populations (Centers for Disease Control and Prevention, 2021h). Without adequate data across all demographic characteristics, there is a possibility that COVID-19 vaccines are being administered to patients who were underrepresented in the vaccine clinical trials.

Purpose

The impact of the COVID-19 pandemic is not uniform across subgroups. Specifically, age, sex, and comorbidity are critical risk factors for mortality of COVID-19 (Qin et al., 2020). In addition, race and ethnicity are clear predictors of severe COVID-19 infection (Mendy et al., 2020). The purpose of this research was to examine the demographic characteristics amongst the participants of the three COVID-19 vaccine clinical trials, which each resulted in an EUA, to understand if subgroups were appropriately represented.

Research Questions

1. Are the demographic characteristics of the participants in the three COVID-19 vaccine trials comparable to those who died due to the COVID-19 virus?

2. Are the demographic characteristics of the participants in the three COVID-19 vaccine trials comparable to the individuals who received a COVID-19 emergency-use-authorized vaccine?

3. Are the demographic characteristics of individuals who received a COVID-19 emergency-use-authorized vaccine comparable to those who died due to COVID-19?

Hypothesis

The hypothesis is that the demographic characteristics of the population that participated in the vaccine clinical trials are more comparable to those who died due to COVID-19, rather than to those who were the first to receive a COVID-19 emergency-use-authorized vaccine.

Methods

First, all demographic characteristics of the study populations, specifically the safety population, enrolled in each phase II/III clinical trial, Pfizer-BioNtech (BNT162b2), Moderna (mRNA-1273-P301), and J&J (VAC31518COV3001), were gathered. The data came from the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing document made available to the public on fda.gov. All three clinical trials were multi-center, randomized, placebo-controlled, and blinded studies, evaluating the efficacy, safety, and immunogenicity of a COVID-19 vaccine. Each trial included thousands of participants from various countries and had different data cutoffs due to the time of EUA request submission.

The VRBPAC briefing document for the Pfizer-BioNtech vaccine contained data from two clinical trials. One of the trials took place in Germany. Therefore, the other clinical trial (study number C4591001) was used in this analysis. The clinical trial had a data cutoff of November 14, 2020, and included participants from the U.S., but also from Argentina, Brazil, Germany, South Africa, and Turkey. The data cutoff date and the list of participating countries was found in the Pfizer-BioNtech, FDA VRBPAC briefing document (U.S. Food and Drug Administration, 2020b, p.12, Table 1).

The Moderna trial, study P301, for safety and efficacy enrolled participants at sites within the United States and had a data cutoff of November 11, 2020. The participating country and the data cutoff date was found in the Moderna, FDA VRBPAC briefing document (U.S. Food and Drug Administration, 2020a, p. 12, section 5.2.1; U.S. Food and Drug Administration, 2020a, p. 21, Table 7).

The J&J trial (study number 3001) for safety and efficacy had a data cutoff of January 22, 2021, and enrolled participants from the U.S., South Africa, and five countries in Latin America.

The list of participating countries and the data cutoff date were found in the J&J VRBPAC briefing document (U.S. Food and Drug Administration, 2021, p. 20, section 5.2.4; U.S. Food and Drug Administration, 2021, p. 7, section 1).

Although this comparative analysis focused on individuals in the United States, the data provided in each VRBPAC briefing document did not separate the study populations by country when summarizing the demographic characteristics. Therefore, the demographic characteristics of the study populations included individuals from other countries.

Second, the demographic characteristics of those that died due to COVID-19 were collected from the CDC COVID Data Tracker, which is provided by the National Center for Health and Statistics (NCHS; Centers for Disease Control and Prevention, 2021a). The datasets are comprised of provisional death counts posted by the CDC, which is considered the most complete and accurate dataset of lives lost due to COVID-19. The provisional death count datasets are based on death certificates and include age, race, ethnicity, gender, comorbidities, and place of death. For this comparative analysis, the deaths reported from the start of the pandemic, January 1, 2020, through June 12, 2021, caused by COVID-19 within the United States were extracted from each of three datasets. A filter was used to extract the deaths that occurred within the United States as the EUAs were granted by the FDA for use solely in this country. The race and ethnicity were extracted from the *Provisional COVID-19 Death by HHS Region, Race and Age* dataset (Centers for Disease Control and Prevention, 2021j). The age and sex were extracted from the *COVID-19 Provisional Counts: Weekly Updates by Select Demographic and Geographic Characteristics* dataset (Centers for Disease Control and Prevention, 2021i). The presence of comorbidities was extracted from the *Conditions*

Contributing to COVID-19 Deaths, by State and Age dataset (Centers for Disease Control and Prevention, 2021n).

Third, the demographic characteristics of individuals who have been fully vaccinated in the United States were collected from the CDC COVID Data Tracker, as well (Centers for Disease Control and Prevention, 2021a, 2021e). For this comparative analysis, the dataset for each demographic (age, sex, race, and ethnicity) was downloaded on July 1, 2021, from the following website: https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic. Those fully vaccinated in the United States between the dates of December 14, 2020, and June 30, 2021, were included. This data was collected by the jurisdiction and was reported to the CDC. The population is comprised of individuals who received a second dose of a two-dose vaccine (Pfizer-BioNTech or Moderna) or one dose of a single-dose vaccine (J&J).

The following demographic characteristics were compared across all three populations: age, sex, race, and ethnicity. The term *sex*, opposed to *gender*, was used in each VRBPAC briefing document. Therefore, the term was utilized throughout this comparative analysis. In addition, comorbidity data was compared across the trial participant population and the COVID-19 death population. However, this data was not available for the population of fully vaccinated individuals. Therefore, this demographic characteristic was descriptively analyzed for discussion only. Appendix B contains a distinct list of the comorbidities of interest from each of the three clinical trials, which profoundly overlap.

Not all demographic characteristics were reported for each individual across the three populations. Therefore, N is equal to the total population and N_r is equal to the total population that the individual demographic characteristic was reported for. N_r was used to calculate each proportion (n%).

All data used in this comparative analysis is summary data and is not individually identifying. There is no interaction of intervention with living individuals, and the data cannot be linked to identifiable inidividuals (living or dead). This research study does not require direct recruitment of human subjects, which, in turn, poses no risk to the population under analysis. In addition, each of the individual sponsors (Pfizer-BioNtech, Moderna, and J&J) submitted their protocols to an institutional review board (IRB) for an ethical review prior to the commencement of their clinical trials.

Limitations

It is important to keep in mind that all existing data on COVID-19 (SARS-CoV-2) is relatively new as it first emerged in December 2019. As each of the three COVID-19 vaccines were recently authorized for emergency use based on interim analyses, there are a limited number of publications about the clinical trials, which restricted the research. It is also important to note that each of the phase III clinical trials have yet to conclude. Therefore, the number of participants that were reported in the VRBPAC briefing documents will not remain the same throughout the closeout of the clinical trials. Participant retention is always difficult, but now that each vaccine is available to the public, it will likely contribute to a rise in subject discontinuations.

Another limitation is the accuracy of the cause-of-death reporting. According to the National Center of Health Statistics (NCHS) guidance for certifying deaths due to COVID-19,

> When a death is due to COVID-19, it is likely the underlying cause of death (UCOD) and thus, it should be reported on the lowest line used in Part I of the death certificate. Ideally, testing for COVID-19 should be conducted, but it is considered acceptable to

> report COVID-19 on a death certificate without this confirmation if the circumstances are compelling within a reasonable degree of certainty. (Centers for Disease Control and Prevention, 2020b, pp. 2-3)

The possibility for over-reporting is probable in these circumstances. The dataset used for this comparative analysis may be incomplete due to the lag in time between when the death occurred and when the death certificate is completed, submitted to NCHS, and processed for reporting purposes. This delay can range from 1 week to 8 weeks or more (Centers for Disease Control and Prevention, 2021g).

The vaccination data collected from the CDC also has its limitations. Unfortunately, not every state and territory reports the demographic characteristics data on the vaccine recipients due to conflicting laws about demographic data collection. For example, Texas does not report demographic-specific information, but they do report the total number of people vaccinated in the state. Therefore, the number of people vaccinated in Texas was removed from *N* resulting in a smaller population of individuals fully vaccinated in the U.S. (Centers for Disease Control and Prevention, 2021g).

Three population groups were formed: (Population I) Vaccine Trial Participants, (Population II) COVID-19 Deaths, and (Population III) Fully Vaccinated Individuals.

The dataset used for Population II: COVID-19 Deaths was not as concise as it was for Population I: Vaccine Trial Participants. Population II required more calculations in order to reach *somewhat* comparable groups. The *Conditions Contributing to COVID-19 Deaths, by State and Age* dataset was comprised of International Classification of Diseases, Tenth Revision (ICD-10) codes. The CDC (2020) explains the reasoning for the use of these codes:

> The International Classification of Diseases (ICD) is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics. This includes providing a format for reporting causes of death on the death certificate. The reported conditions are then translated into medical codes through use of the classification structure and the selection and modification rules contained in the applicable revision of the ICD, published by the World Health Organization (WHO). These coding rules improve the usefulness of mortality statistics by giving preference to certain categories, by consolidating conditions, and by systematically selecting a single cause of death from a reported sequence of conditions. The single selected cause for tabulation is called the underlying cause of death, and the other reported causes are the non-underlying causes of death. The combination of underlying and non-underlying causes is the multiple causes of death.

The ≥ *1 comorbidity* group was calculated by subtracting individuals that had an ICD 10 code of at least one of the following: S00-T88, V01-X59, X60-X84, X85-Y09, Y10-Y36, Y40-Y89, and/or U01-U03 (Intentional and unintentional injury, poisoning, and other adverse events) from the total number of individuals with an ICD 10 code of U07.1 (COVID-19) and ≥ 1 comorbidity. The preceding ICD-10 codes are defined in Appendix C.

Analysis

Microsoft Excel (2012) functionality was used to consolidate, organize, calculate, and graph the demographic characteristics of the three populations. Graphical and numerical descriptive methods were used to summarize the key demographic characteristics across all populations.

To answer research Question One --- "Are the demographic characteristics of the participants in the three COVID-19 vaccine trials representative of deaths due to the COVID-19 virus?" --- the following populations were compared: (Population I) Vaccine Trial Participants and (Population II) COVID-19 Deaths. The proportion of vaccine trial participants belonging to each demographic characteristic will be directly compared to the proportion of the same demographic characteristic in the COVID-19 death population. For example, the proportion of males in the vaccine trial participant population was compared to the proportion of males that have died due to COVID-19 and again to those who are fully vaccinated.

To answer Research Question Two --- "Are the demographic characteristics of the participants in the three COVID-19 vaccine trials representative of individuals who received a COVID-19 emergency use authorized vaccine?" --- the following populations were compared: (Population I) Vaccine Trial Participants and (Population III) Fully Vaccinated Individuals. The proportion of vaccine trial participants belonging to each demographic characteristic was directly compared to the proportion of the same demographic characteristic for the individuals fully vaccinated.

To answer Research Question Three --- "Are the demographic characteristics of the COVID-19 death population representative of individuals who received a COVID-19 emergency-use-authorized vaccine?" --- the following populations were compared: (Population II) COVID-19 Deaths and (Population III) Fully Vaccinated Individuals. The proportion of the individuals fully vaccinated belonging to each demographic characteristic was directly compared to the proportion of the same demographic characteristic for the COVID-19 death population.

To determine if the diversity of the vaccine trial participant population (Population I) is overall representative of the diversity of COVID-19 deaths (Population II) and/or those that are fully vaccinated (Population III), a simplified correlation table was employed to test the hypothesis. The hypothesis is that the demographic characteristics of the population that participated in the vaccine clinical trials are more representative of those who died due to COVID-19 rather than those who were first to receive a COVID-19 emergency-use-authorized vaccine. Each demographic characteristic proportion was compared across the three populations. The two proportions with the smallest difference were assigned a "1" and the remaining population was assigned a "0". After this was complete for each demographic characteristic, the columns were totaled. The two populations with the highest totals were considered more comparable to each other.

Results

Three populations and their available demographic characteristics were identified:

- Population I: Vaccine Trial Participants
    - The total safety population in each clinical trial was combined for a total of 114,410 participants.
- Population II: COVID-19 Deaths
    - As of June 16, 2021, a total of 590,091 COVID-19 related deaths were reported within the United States between January 1, 2020, and June 12, 2021.
- Population III: Fully Vaccinated Individuals
    - From December 14, 2020, through June 30, 2021, a total of 154,884,686 individuals have been fully vaccinated within the United States.

Population I is comprised of demographic characteristics from all three vaccine clinical trials, depicted in Tables 1-3. The following demographics were included for each population, sex, age, race, and ethnicity.

Table 1

Demographic Characteristics of the Pfizer-BioNtech Clinical Trial Participants

Demographic Characteristic		Total Number
Age	≥ 18 to < 65	31416
	≥ 65	8613
Sex	Male	20376
	Female	19901
Race	American Indian or Alaska Native	253
	Asian	1763
	Black or African American	3929
	Native Hawaiian or other Pacific islander	83
	White	33006
	Other/Not Reported	227
	Multiracial	1016
Ethnicity	Hispanic or Latino	10553
	Not Hispanic or Latino	29499
High Risk Comorbidities	≥ 1 comorbidity	18592
	None	21685

Note. Adapted from *FDA Briefing Document Pfizer-BioNTech COVID-19 Vaccine* (p. 20), by U.S. Food and Drug Administration, 2020, (https://www.fda.gov/media/144245/download).

Table 2

Demographic Characteristics of the Moderna Clinical Trial Participants

Demographic Characteristic		Total Number
Age	≥ 18 to < 65	22830
	≥ 65	7520
Sex	Male	15995
	Female	14355
Race	American Indian or Alaska Native	230
	Asian	1385
	Black or African American	3090
	Native Hawaiian or other Pacific islander	66
	White	24023
	Other/Not Reported	636
	Multiracial	634
Ethnicity	Hispanic or Latino	6234
	Not Hispanic or Latino	23834
High Risk Comorbidities	≥ 1 comorbidity	6742
	None	23608

Note. Adapted from *FDA Briefing Document Moderna COVID-19 Vaccine* (p. 21), by U.S. Food and Drug Administration, 2020, (https://www.fda.gov/media/144434/download).

Table 3

Demographic Characteristics of J&J Clinical Trial Participants

Demographic Characteristic		Total Number
Age	≥ 18 to < 65	35222
	≥ 65	8561
Sex	Male	24053
	Female	19722
Race	American Indian or Alaska Native	4143
	Asian	1430
	Black or African American	8515
	Native Hawaiian or other Pacific islander	106
	White	25696
	Other/Not Reported	623
	Multiracial	2449
Ethnicity	Hispanic or Latino	19837
	Not Hispanic or Latino	22834
High Risk Comorbidities	≥ 1 comorbidity	17858
	None	25925

Note. Adapted from *FDA Briefing Document Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19* (p. 22), by U.S. Food and Drug Administration, 2020, (https://www.fda.gov/media/146217/download).

The presence of at least one comorbidity was captured in each clinical trial as shown in Tables 1-3. However, comorbidity data for Population III: Fully Vaccinated Individuals is not available. The total count and proportion of each demographic characteristic across all three populations is shown in Table 4, where the first column, Population I: Vaccine Trial Participants is comprised of data from Tables 1-3.

Table 4

Summary of Demographic Characteristics Across All Three Populations

	Population I: Vaccine Trial Participants (N^a=114,410) n (%)	Population II: COVID-19 Deaths (N=590,091) n (%)	Population III: Fully Vaccinated (N=154,884,686) n (%)
Age			
	N_r^b=114,162	*N_r=589,769*	*N_r=136,948,339*
≥ 18 to < 65	89,468 (78.2)	120,199 (20.4)	97,048,829 (70.9)
≥ 65	24,694 (21.6)	469,570 (79.6)	39,899,510 (29.1)
Sex			
	N_r=114,402	*N_r=N*	*N_r=141,675,981*
Female	53,978 (47.2)	266,480 (45.2)	75,053,468 (47.0)
Male	60,424 (52.8)	323,611 (54.8)	66,622,513 (53.0)
Race			
	N_r=113,303	*N_r=481,395*	*N_r=82,494,562*
American Indian or Alaska Native	4,626 (4.0)	6,667 (1.1)	899,877 (1.1)
Asian	4,578 (4.0)	22,616 (3.8)	6,031,703 (7.3)
Black or African American	15,534 (13.6)	88,857 (15.1)	8,541,996 (10.4)
Native Hawaiian or other Pacific islander	255 (0.2)	1,083 (0.2)	273,413 (0.3)
White	82,725 (72.3)	358,263 (60.7)	59,020,327 (71.5)
Multiracial/ Other/ Unknown	5,585 (4.9)	3,909 (0.8)	7,727,246 (9.4)
Ethnicity			
	N_r=112,791	*N_r=588,109*	*N_r=96,587,754*
Hispanic or Latino	36,624 (32.0)	108,695 (18.4)	14,093,192 (14.6)
Not Hispanic or Latino	76,167 (66.6)	479,414 (81.2)	82,494,562 (85.4)
Comorbidities			
	N_r=N	*N_r=N*	
≥ 1 comorbidity	43,192 (37.8)	576,610 (97.7)	-
None	71,218 (62.2)	13,481 (2.3)	-

[a] *N* is equal to the total number of individuals in the population

[b] N_r is equal to the total number of individuals that reported the demographic characteristics

Note. Adapted from *Provisional COVID-19 Deaths by HHS Region, Race, and Age*, *Conditions Contributing to COVID-19 Deaths, by State and Age*, *Provisional COVID-19 Deaths by Sex and Age, Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States*, by Centers for Disease Control and Prevention, 2021j, 2021m, 2021k, 2021e.

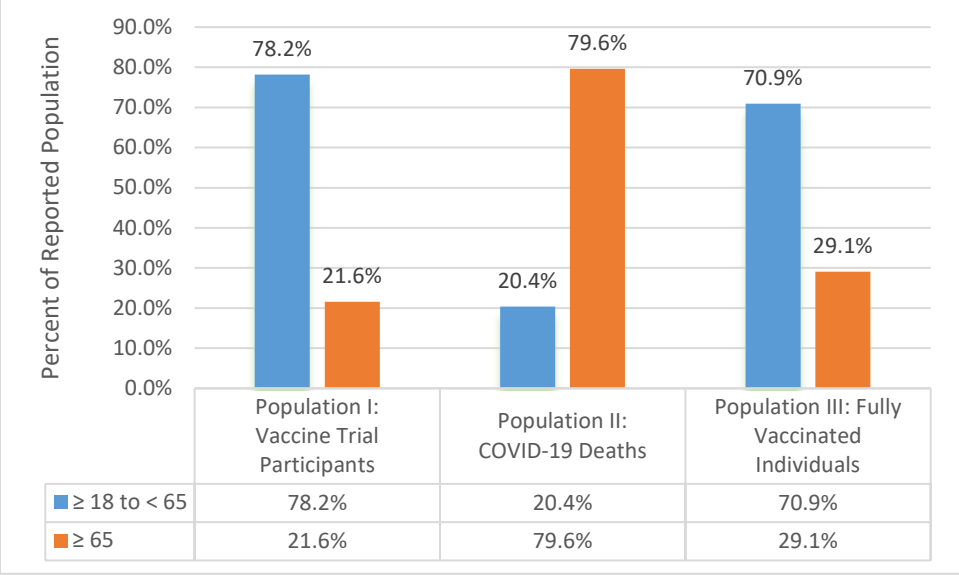
Age

The ages used in this analysis were divided into two groups, which each have a sizeable range. The two ranges used for this comparative analysis were ≥ 18 to < 65 years old and ≥ 65 years old.

Age distribution was similar in Population I: Vaccine Trial Participants and Populations III: Fully Vaccinated Individuals, but significantly different in Population II: COVID-19 Deaths. Age was reported for 114,162 individuals in Population I; 589,769 in Population II; and 136,948,339 in Population III (N_r) as shown in Table 4. There was a higher percentage of individuals in the ≥ 18 to < 65-year-old range in Population I and Population III (78.2% and 70.9%, respectively), than in Population II (20.4%). Population II is made of 79.6% of individuals aged 65 years or older as shown in Figure 1.

Figure 1

Distribution of Age Across Populations



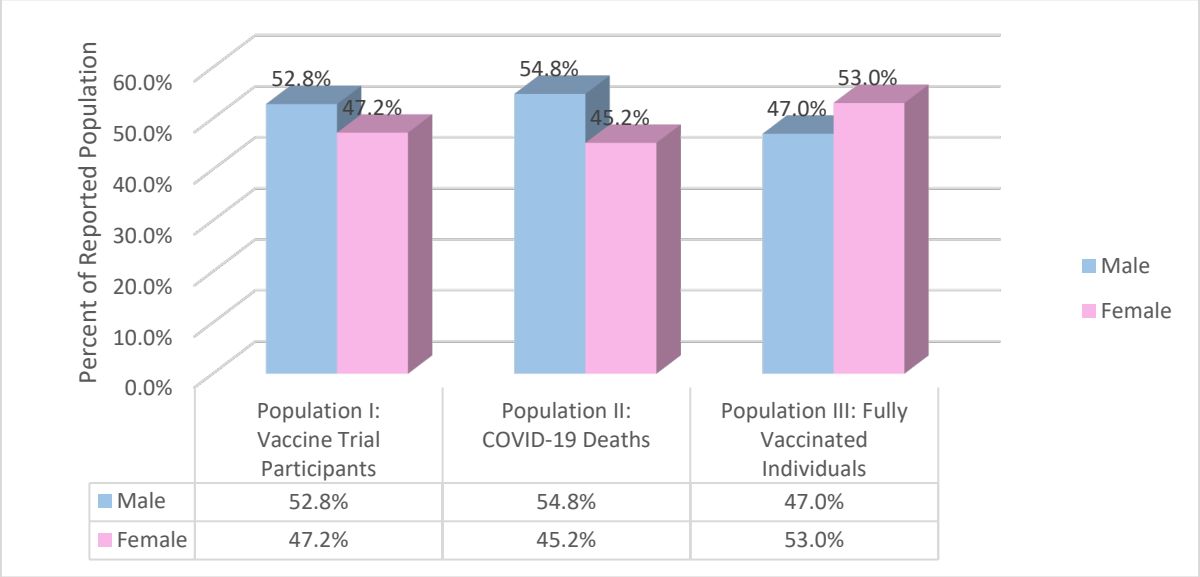
Sex

The sex of each individual across the three populations was reported as male or female with the exception of eight participants from the J&J vaccine clinical trial. Of those eight participants, six were categorized as Undifferentiated and two were categorized as Unknown. Since only male and female categories were reported for Populations II and III, these eight participants were removed from the analysis.

Sex was reported for 114,402 trial participants; 590,091 COVID-19 deaths; and 141,675,981 fully vaccinated individuals (N_r) as male or female as shown in Table 4. Overall, there were slightly more male participants than female participants in both the vaccine trial participant population (52.8%) and the COVID-19 death population (54.8%). However, there were slightly fewer male participants in the fully vaccinated population (47%) as shown in Figure 2.

Figure 2.

Distribution of Sex Across Populations



	Population I: Vaccine Trial Participants	Population II: COVID-19 Deaths	Population III: Fully Vaccinated Individuals
Male	52.8%	54.8%	47.0%
Female	47.2%	45.2%	53.0%

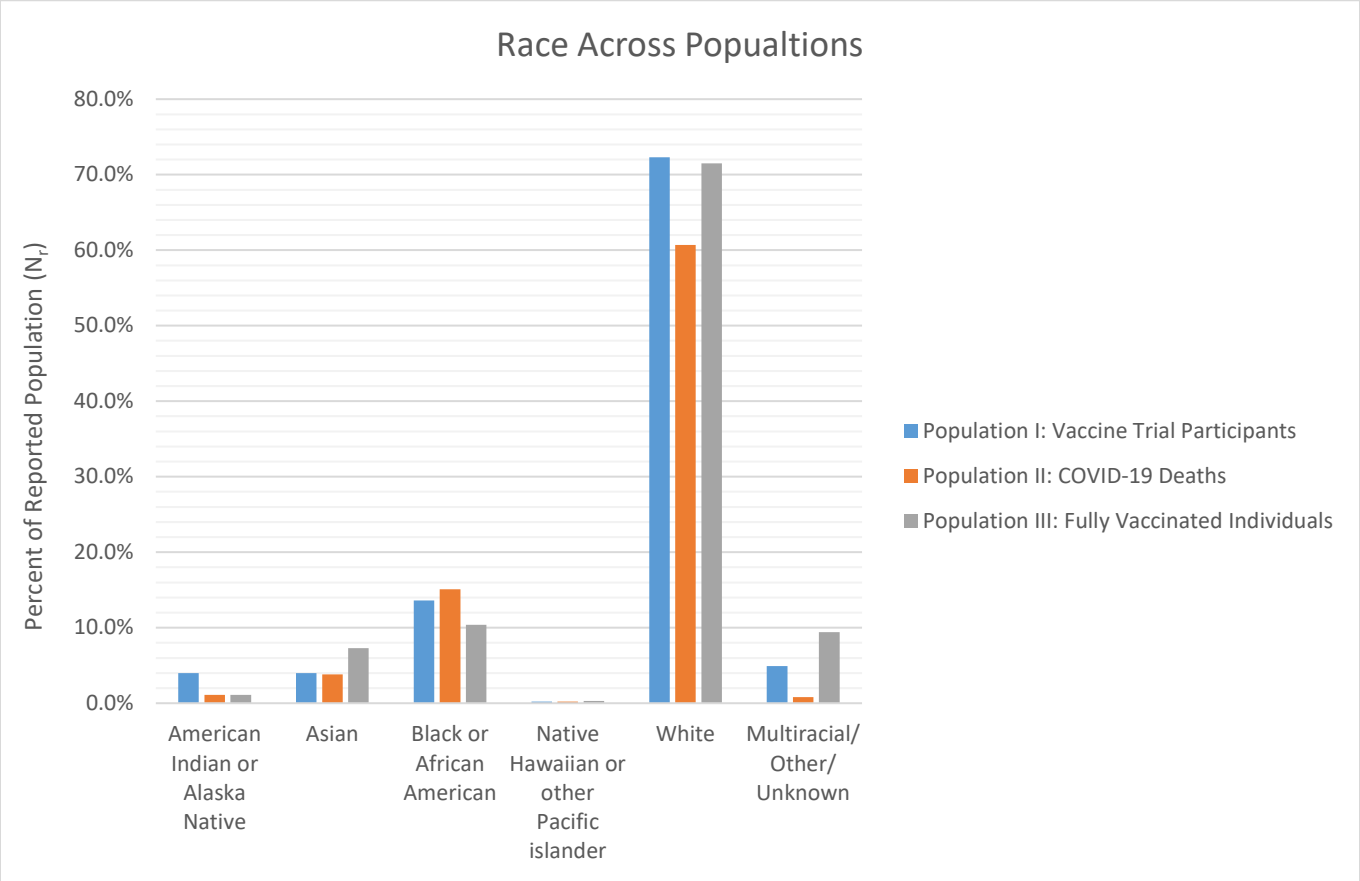
Race

Population I: Vaccine Trial Participants and Population II: COVID-19 Deaths used seven categories to report race: (a) American Indian or Alaska Native, (b) Asian, (c) Black or African American, (d) Native Hawaiian or other Pacific islander, (e) White, (f) Other/Unknown and (g) Multiracial. However, the dataset for Population III: Fully Vaccinated Individuals was comprised of six categories, with the sixth category comprising of other/unknown and multiracial individuals. Therefore, the other/unknown and multiracial categories were manually combined across the remaining two populations, resulting in six racial categories across all three populations.

As shown in Table 4, race was reported for 113,303 individuals in Population I: Vaccine Trial Participants; 481,395 in Population II: COVID-19 Deaths; and 82,494,562 in Population III: Fully Vaccinated Individuals (N_r,). White individuals accounted for the highest proportion in all three populations as shown in Figure 3. However, the proportion of White individuals in Population II: COVID-19 Deaths is lower (60.7%) than in Populations I & III (72.3% and 71.5%, respectively). Black or African Americans accounted for the second highest proportion in all three populations. However, opposite from the White population, Blacks or African Americans had lower proportions in Populations I &III (13.6% and 10.4%) than in Population II (15.1%). Individuals who were reported as multiracial/other/unknown is low in Population II (0.8%), but higher in Populations I & III (4.9% and 9.4%, respectively). Figure 3 displays the proportion of race across all the three populations.

Figure 3

Distribution of Race Across Populations

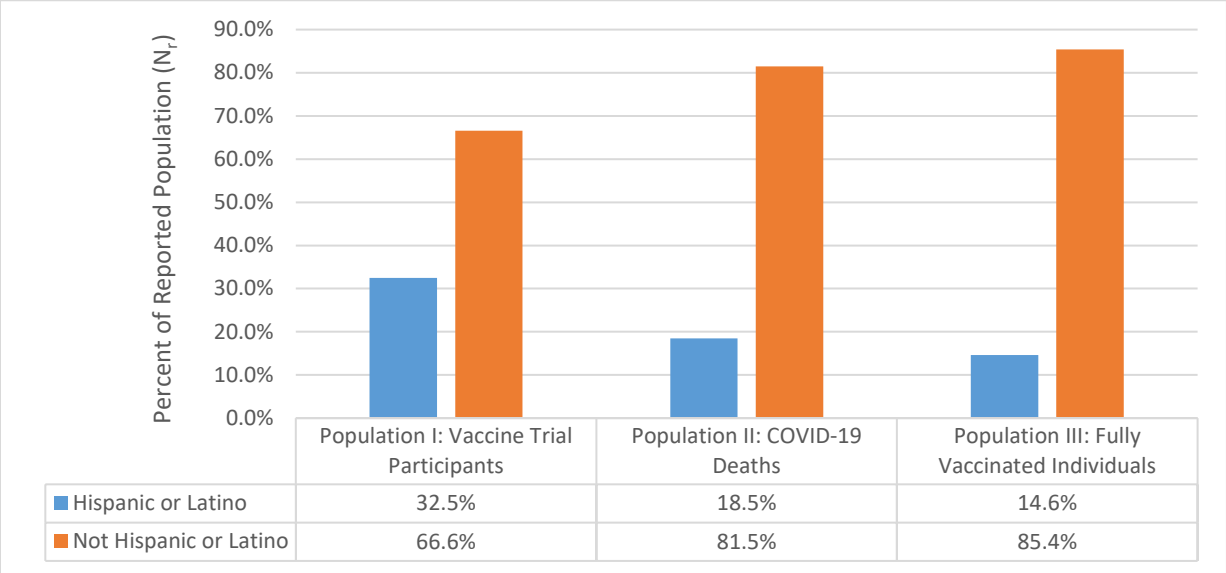


Ethnicity

All three populations were categorized by ethnicity: Hispanic or Latino and Not Hispanic or Latino. As shown in Table 4, race was reported for 112,791 individuals in Population I: Vaccine Trial Participants; 588,109 in Population II: COVID-19 Deaths; and 96,587,754 in Population III: Fully Vaccinated Individuals (N_r,). All three populations include more Not Hispanic or Latino than Hispanic or Latino individuals. Population I has the highest Hispanic or Latino proportion (32.5%) as well as the lowest proportion of Not Hispanic or Latino individuals (66.6%). Figure 4 illustrates the distribution of ethnicity across each of the three populations.

Figure 4

Distribution of Ethnicity Across Populations



Comorbidities

Table 5 shows the calculation used to reach the number of individuals that died due to the COVID-19 virus with one or more comorbidities

Table 5

Population II Comorbidity Calculation

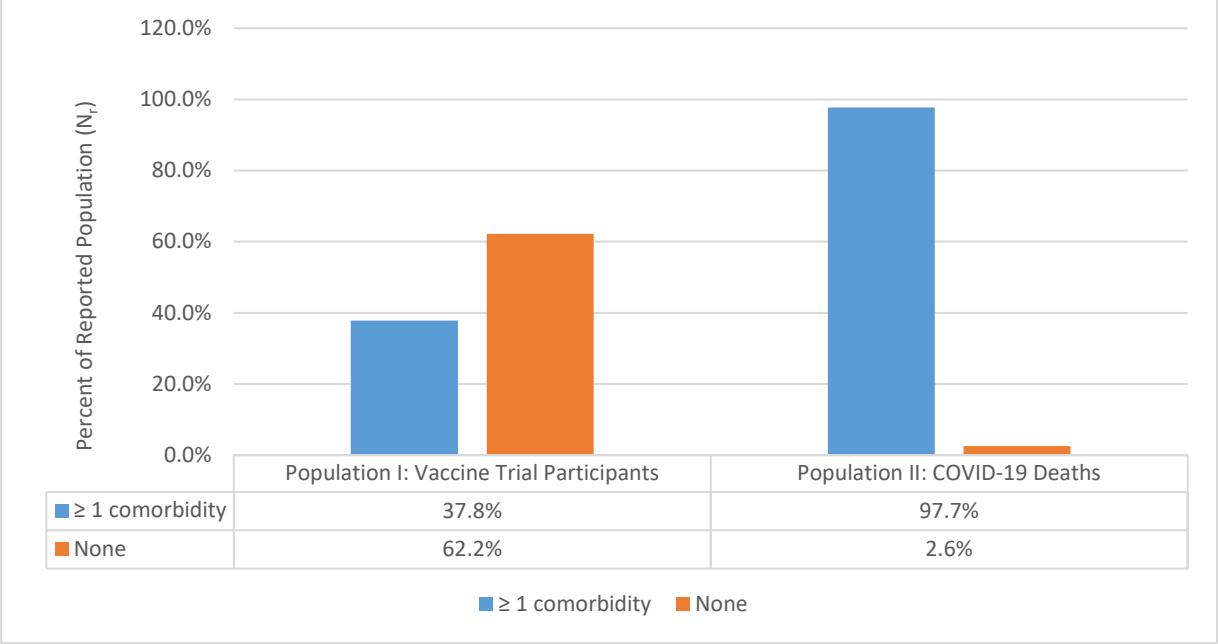
Total Deaths with an ICD-10 code U07.1(COVID-19) and at least one other ICD-10 code (i.e. comorbidity)[c]	588,577
Total Deaths with an ICD-10 code U07.1 (COVID-19) and at least one of the following: S00-T88, V01-X59, X60-X84, X85-Y09, Y10-Y36, Y40-Y89, U01-U03[d]	-11,967
Population II: COVID-19 Deaths ≥1 or more comorbidity	576,610

[c]Appendix A contains a full list of comorbidities reported in conjunction with COVID-19 (ICD-10 code U07.1).
[d]Appendix C contains the corresponding disease for each of the ICD-10 codes removed from the analysis.

Presence of a comorbidity was reported for 114,410 individuals in Population I: Vaccine Trial Participants and 590,091 in Population II: COVID-19 Deaths as shown in Table 4. Figure 5 shows a significantly higher proportion with one or more comorbidities in the COVID-19 death population, 97.7%, than in vaccine trial participants, 37.8%.

Figure 5

Distribution of Comorbidities Between Vaccine Trial Participants and COVID-19 Deaths



Overall Comparison

Table 6 was created to compare demographic characteristics individually across all three populations. Specifically, it shows that the demographic characteristics of the participants in the three COVID-19 vaccine trials (Population I) are more comparable to those who died due to the COVID-19 virus (Population II) than to individuals who have been fully vaccinated (Population III).

1. The demographic characteristics of the participants in the three COVID-19 vaccine trials (Population I) and to those who died due to the COVID-19 virus (Population II) are comparable for most demographic characteristic categories. Age is the only demographic characteristic that is not comparable between these two populations.

2. The demographic characteristics of the participants in the three COVID-19 vaccine trials (Population I) are somewhat similar to the individuals who received a COVID-19 emergency-use-authorized vaccine (Population III). Sex, as well as many racial groups, is not comparable between these two populations.

3. The demographic characteristics of those who died due to the COVID-19 virus (Population II) is not completely representative of the individuals who were fully vaccinated. Again, racial groups and age are not comparable between these two populations.

Table 6

Overall Comparison of Demographic Characteristics Across All Three Populations

		Population I: Vaccine Trial Participants	Population II: COVID-19 Deaths	Population III: Fully Vaccinated
Age				
	≤ 18 - 64	1	0	1
	≤ 65	1	0	1
Sex				
	Male	1[c]	1	0
	Female	1	1	0
Race				
	American Indian or Alaska Native	0	1	1
	Asian	1	1	0
	Black or African American	1	1	0
	Native Hawaiian or other Pacific islander	1	1	0
	White	1	0	1
	Other/Not Reported/multiracial	1	1	0
Ethnicity				
	Hispanic or Latino	0	1	1
	Not Hispanic or Latino	0	1	1
	TOTAL	9	9	6

[c] The two proportions with the smallest difference were assigned a "1" and the remaining population was assigned a "0".

Discussion

The purpose of this study was to compare the demographic variables of three populations, COVID-19 Vaccine Trial Participants, COVID-19 Deaths, and Individuals Vaccinated for COVID-19, to determine if the trial participants were appropriately representative. The demographic characteristics of the vaccine clinical trials participants were comparable to those who died due to COVID-19, but less comparable to those who were the first to receive a COVID-19 emergency-use-authorized vaccine.

Age

The age distribution across the three populations differed significantly. The vaccine trial participant population (Population I) is comparable to the population of individuals fully vaccinated (Population III). However, Population II: COVID-19 Deaths is entirely inverse of the other two populations (Populations I & III).

As AE reports seem to be occurring in smaller subgroups (e.g., myocarditis and pericarditis in individuals under 30 years old, TTS in individuals under 50 years old), organizing the age data into smaller ranges would be of great value (e.g., ages 16-20, 21-30, 31-40; Centers for Disease Control and Prevention, 2021n). Due to the predetermined ranges presented in each VRBPAC briefing document, it was impossible to divide the age ranges further across all three populations. Of course, this would be possible with the full dataset from each clinical trial and would be valuable to analyze in future research. Although it is reassuring from a safety standpoint that the participants included in the vaccine clinical trials represent the age range of the population fully vaccinated, it is evident that the elder population needs the most aid when it comes to surviving COVID-19.

Sex

The results suggest that men and women were equally represented across all three populations. The slightly higher proportion of women receiving a COVID-19 vaccination first may be due to the vaccine allocation plan which prioritized healthcare personnel (Dooling, et al., 2020).

Race & Ethnicity

Population I: Vaccine Trial Participants were overall racially representative of Population II: COVID-19 Deaths *and* Population III: Individuals Fully Vaccinated. However, there are a few obvious outliers. Black or African Americans are the only racial group with a smaller proportion in Population I *and* Population III, than in Population II. Although there is a higher proportion of Blacks and African Americans dying due to the COVID-19 virus, they may not be as willing to participate in clinical trials or voluntarily receive a vaccination that has yet to be fully approved. This data may suggest that mistrust in the medical community still exists. In recent surveys, experience with racial discrimination is a key predictor of COVID-19 vaccine hesitancy (Savoia et al., 2021). Similarly, Black individuals are less likely to participate in other vaccine trials (e.g., HIV vaccine trials) due to misinformation, fear and mistrust, and overall stigma (Moutsiakis & Chin, 2007). With the unfortunate circumstances of racism in clinical trial history, the medical community has yet to regain trust of Blacks and African Americans.

Native Hawaiians or other Pacific islanders only represent 0.2% of the vaccine trial participant population (Population I), which translates to a total of only 255(n) participants spanning all three vaccine trials (N_r = 113,303). Although the proportion closely compares to the

subgroup in Population III (0.3%), approximately 273,413(n) Native Hawaiians or other Pacific islanders are fully vaccinated via an EUA vaccine.

Similarly, Asians make up 4% of the vaccine trial participant population (Population I) which converts to a total 4,578(*n*) participants spanning all three vaccine trials (N_r = 113,303). The proportion of individuals in Population III (N_r = 82,494,562) is almost two-fold (7.3%) the proportion of Asians in Population I. Precisely 6,031,703(n) Asian Americans have been fully vaccinated via an EUA vaccine. Given that an individual from Population III received a vaccination from only one of the three authorized vaccines, it may be of value to compare *n* from Population III with the average of the total number of Asians in each vaccine clinical trial from Tables 1-3. Although the proportions (4% and 7.3%) don't seem like a significant difference, the total numbers (*n*) may be more telling.

Although the ethnicity represented in each population was extremely similar, there was a noticeable trend in Figure 4. As the proportion of Hispanic or Latinos decreased across the three populations, the proportion of Not Hispanic or Latinos increased.

Comorbidities

As underlying health conditions can play a role in the severity of COVID-19, all three clinical trials had the intention of including these groups during recruitment. Unfortunately, during the data collection new limitations surfaced. This data was not available for Population III and the data available for Population II was not concise. It is common for multiple ICD-10 codes to be used in death reports to capture both the chain-of-event conditions and significant contributing conditions. As such, combining or removing certain subcategories based on the ICD-10 codes in this dataset will result in counting a single death multiple times. The only group

that seemed reasonable to completely remove from the analysis was the "Intentional and unintentional injury, poisoning, and other adverse events." This was done for two reasons: (a) None of the corresponding ICD-10 codes, S00-T88, V01-X59, X60-X84, X85-Y09, Y10-Y36, Y40-Y89, U01-U03, are likely to increase the severity of COVID-19, nor are they considered an underlying medical condition, and (b) The survival of COVID-19 is unknown if the accidental death due to an external cause did not occur. Corresponding diseases and injuries for the preceding ICD-10 codes are listed in Appendix C. In the future, it would be valuable to explore the number of individuals in each comorbidity subset and compare the populations again. For example, Gundlapalli et al. (2021) reported obesity as one of the least common significant contributing conditions listed on death certificates (2.7%), but obesity accounted for 28.5% of participants in the J&J clinical trial and 70% of those with at least one comorbidity. Taking this into account, the demographic characteristic of one or more comorbidities in the vaccine trial population (Population I) is not representative of deaths due to the COVID-19 virus (Population II). Without data about comorbidities in the individuals fully vaccinated, reports made through VAERS will be the only way to capture potential risks for individuals with specific comorbidities.

Each clinical trial used in this analysis will continue to follow participants for two years after receiving the vaccine (U.S. Food and Drug Administration, 2020a, 2020b, 2021). Some demographic subgroups were underrepresented during the interim analyses. For the groups that were sufficiently represented in the clinical trials, potential loss of participants to follow-up could result in more underrepresented groups when it is time for the final analysis.

Conclusion

The purpose of this study was to compare the demographic variables of three populations, COVID-19 Vaccine Trial Participants, COVID-19 Deaths, and Individuals Vaccinated for COVID-19, to determine if the trial participants were appropriately representative. The demographic characteristics of the vaccine clinical trials participants were comparable to those who died due to COVID-19, but less comparable to those who were the first to receive a COVID-19 emergency-use-authorized vaccine.

Each clinical trial used in this analysis will continue to follow participants for two years after receiving the vaccine (U.S. Food and Drug Administration, 2020a, 2020b, 2021). Some demographic subgroups were underrepresented during the interim analyses and potential loss of participants to follow up could result in more underrepresented groups when it is time for the final analysis.

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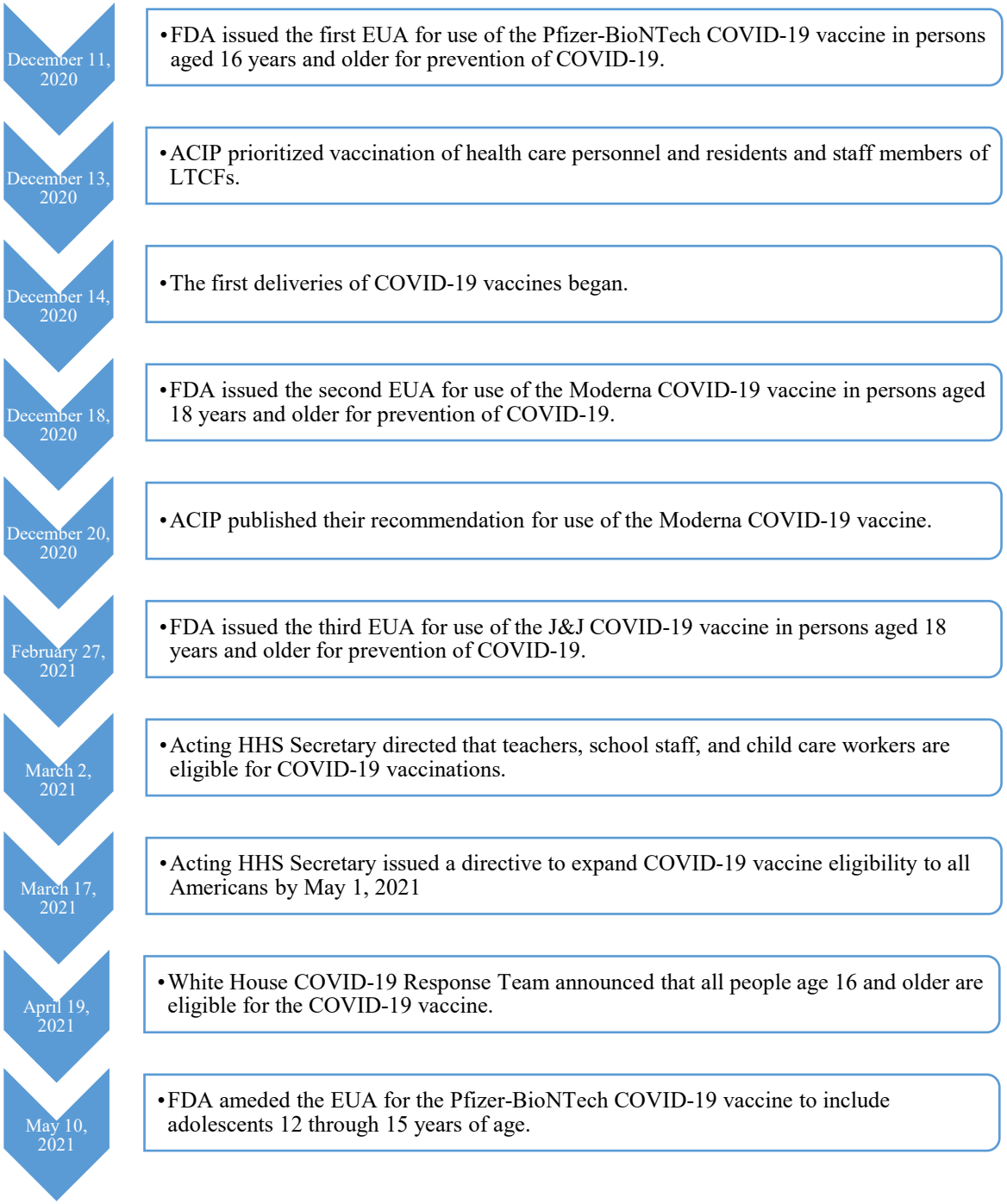
APPENDICES

Appendix A: Timeline of Vaccine Distribution



Note. Adapted from *COVID-19 vaccine distribution: The process*, by Assistant Secretary for Public Affairs, 2021, (https://www.hhs.gov/coronavirus/covid-19-vaccines/distribution/index.html).

Appendix B: List of Comorbidities

Each clinical trial incorporated participants with comorbidities in their safety population. Below is the list of comorbidities considered in each trial, as well as the list included in the COVID-19 death population (Population 2).

J&J (VAC31518COV3001)

Comorbidities associated with an increased risk of progression to severe COVID-19.

- Asthma
- Cancer
- Cerebrovascular disease
- Cystic fibrosis
- Chronic kidney disease
- COPD
- Serious heart conditions
- Human Immunodeficiency Virus (HIV) infection
- Hypertension
- Immunocompromised state (blood/organ txp)
- Liver disease
- Neurologic conditions
- Obesity
- Pulmonary fibrosis
- Sickle cell disease
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Thalassemia

Moderna (mRNA-1273-P301)

Presence of one or more of the following comorbidities was used to label a participant as high risk:

- Chronic lung disease
- Emphysema and chronic bronchitis,
- Idiopathic pulmonary fibrosis
- Cystic fibrosis
- Asthma (moderate- severe)
- Significant cardiac disease
- Heart failure
- Coronary artery disease
- Congenital heart disease
- Cardiomyopathies
- Pulmonary hypertension
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human Immunodeficiency Virus (HIV) infection

Pfizer-BioNtech (C4591001)

The number of participants who have at least 1 comorbidity that increases the risk of severe COVID-19 disease: defined at patients who had at least one of the Charlson comorbidity index category or obesity only (BMI $\geq$ 30 km/m^2).

Charlson Comorbidity Index which is based on a list of 19 conditions identified from diagnosis in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a great level of comorbidity.

- Cancer
- Metastatic Carcinoma
- Chronic Pulmonary Disease
- Congestive Heart Failure
- Cerebrovascular Disease
- Dementia
- Renal Disease
- Peripheral Vascular Disease
- Myocardial Infarction
- Paraplegia and Hemiplegia
- Connective Tissue Disease- Rheumatic Disease
- Peptic Ulcer Disease
- Diabetes without Complications
- Diabetes with Complications
- Mild, Moderate, or Severe Liver Disease
- HIV/AIDS

COVID-19 Mortality

- Influenza and pneumonia
- Chronic lower respiratory diseases
- Adult respiratory distress syndrome
- Respiratory failure
- Respiratory arrest
- Other diseases of the respiratory system
- Hypertensive diseases
- Ischemic heart disease
- Cardiac arrest
- Cardiac arrhythmia
- Heart failure
- Cerebrovascular diseases
- Other diseases of the circulatory system
- Sepsis
- Malignant neoplasms
- Diabetes
- Obesity
- Alzheimer disease
- Vascular and unspecified dementia
- Renal failure
- Intentional and unintentional injury, poisoning, and other adverse events
- All other conditions and causes (residual)

Appendix C: ICD-10 Codes and Corresponding Diseases and Injuries

Table 7

ICD-10 Codes Referenced Within

S00-T88	Injury, poisoning and certain other consequences of external causes
U01-U02	Terrorism or Sequelae of terrorism
U03	Unintentional self-harm (suicide)
U07.1	COVID-19
V01-Y89	External causes of morbidity

Note. Adapted from *2021 ICD-10*, by U.S. Centers for Medicare and Medicaid Services. 2020, (https://www.cms.gov/medicare/icd-10/2021-icd-10-pcs).

Appendix D: List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
ASPA	Assistant Secretary for Public Affairs
AE	adverse event
AIDS	acquired immunodeficiency syndrome
CDC	Center for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
HHS	Health and Human Services
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases
LTCF	Long-Term Care Facility
NCHS	National Center for Health Statistics
NIH	National Institute of Health
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TTS	thrombosis with thrombocytopenia syndrome
VAERS	Vaccine Adverse Event Reporting System
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization